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Palladium-Catalyzed Decarboxylative Asymmetric Allylic Alkylation of 1,4-Diazepan-5-ones

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Abstract

We report the palladium-catalyzed asymmetric allylic alkylation of 1,4-diazepan-5-ones. This reaction proceeds smoothly to give *gem*-disubstituted diazepanone heterocycles bearing various functional groups in up to >99% yield and up to 95% ee. An electron-rich *p*-anisoyl lactam protecting group and the use of a nonpolar solvent proved crucial to obtaining high enantioselectivity in most cases. Additionally, we demonstrate the use of our methodology in the synthesis of a *gem*-disubstituted analogue of the FDA-approved anti-insomnia drug suvorexant.

Graphical Abstract

Diazepane heterocycles are common structural motifs found in a variety of pharmaceuticals, including the benzodiazepine anxiolytics,¹ the antipsychotic clozapine,² and the novel anti-insomnia drug suvorexant (Figure 1).³ Notably, many of these compounds lack C sp³ complexity—suvorexant is a notable exception as the only FDA-approved drug bearing a stereodefined chiral center in a diazepane ring. The lack of stereochemically complex diazepanes in the drug landscape, especially those bearing all-carbon quaternary stereocenters, is likely due to a lack of asymmetric methods available for their synthesis, leading to a reliance on kinetic resolution, either of a quaternary building block or of the diazepane itself.⁴ New methods to synthesize such stereodefined diazepanes are desirable, as a higher degree of saturation and the presence of chiral centers in drug molecules

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03530. Experimental procedures, characterization data for all new compounds, and NMR and IR spectra (PDF)

The authors declare no competing financial interest.

are correlated with greater clinical success and potentially fewer off-target effects, which can be attributed to a greater number of accessible 3D conformers.⁵ Thus, the efficient and enantioselective incorporation of *gem*-disubstitution into diazepane heterocycles could enable the development of pharmaceutical agents with enhanced properties. Furthermore, increasing substitution on the diazepane ring could potentially block metabolically labile sites, thus improving the pharmacokinetic profile of a molecule.

Palladium-catalyzed decarboxylative asymmetric allylic alkylation represents a promising method for the synthesis of enantioenriched *gem*-disubstituted diazepane derivatives. Since the initial report by our laboratory describing the asymmetric synthesis of quaternary centersubstituted carbonyl compounds,⁶ this method has been extended to a wide variety of carbocyclic and heterocyclic scaffolds by our group, the Trost group, and others.^{7,8} Generally, simple lactams perform exceptionally well in this reaction, with the high enantioselectivities observed for this substrate class being attributable to a combination of steric and electronic effects of the lactam protecting group.^{7b,c} In contrast, heterocycles that bear multiple nitrogen atoms have been less commonly utilized.

Recently, our group reported the enantioselective synthesis of *gem*-disubstituted *N*-Boc diazaheterocycles via palladium-catalyzed decarboxylative asymmetric allylic alkylation (Scheme 1a).^{7e} This reaction possesses excellent functional group tolerance and delivers a variety of *gem*-disubstituted piperazines in high yields and enantioselectivities. One example of a diazepanone as a substrate for palladium-catalyzed decarboxylative asymmetric allylic alkylation was published by our group in 2015, but only a modest ee of 59% was achieved (Scheme 1b).^{7d} We now report our successful efforts utilizing palladium-catalyzed decarboxylative asymmetric allylic alkylation to synthesize a variety of *gem*-disubstituted diazepanones in high yields and enantioselectivities.

Starting from the commercially available lactam 1, substrates for palladium-catalyzed decarboxylative asymmetric allylic alkylation were readily accessible in a 3-step sequence analogous to that previously reported by our group (Scheme 2).^{7e} *N*-Acylation of 1 with an acyl chloride, followed by C-acylation with allyl cyanofornate, yielded allyl ester 2. Subsequent functionalization of 2 was conducted with a variety of electrophiles, giving substrates 3a–l which bear diverse functional groups. The divergence put in place by latestage functionalization of dicarbonyl 2 could enable rapid analoging in the context of medicinal chemistry. In prior research by our group, the use of a Boc carbamate protecting group proved key to an efficient, functionally diverse substrate synthesis by presumably lowering the amine's nucleophilicity and thereby reducing unproductive side reactions.^{7e}

We began by examining conditions for the asymmetric allylic alkylation of diazepanone 3a ($R^2 = \text{Bn}$), utilizing $\text{Pd}_2(\text{pmdba})_3$ as a palladium source and (*S*)-(CF₃)₃-*t*-BuPHOX as a chiral ligand (Table 1). Generally, polar solvents led to only modest ee of the enantioenriched product 4a (entries 1–3). In prior research by our laboratory, 2:1 hexanes/toluene proved to be a robust solvent system for achieving high ee with a variety of lactam substrates.^{7e} Indeed, an ee of 87% was obtained for compound 4a under these conditions (entry 6). Finally, we were pleased to discover that an even more nonpolar solvent, methylcyclohexane,⁹ further enhanced enantioselectivity, yielding 4a in 89% ee

(entry 9). Despite its lack of polarity, methylcyclohexane still resulted in homogeneous reaction mixtures, and both of these values were replicable within 1% ee in quadruplicate. In the course of examining reaction conditions, we also discovered that use of the highly electron-deficient ligand (*S*)-Ty-PHOX¹⁰ resulted in a drop in ee (entry 8). This is in contrast with previous results indicating that more electron-deficient ligands often give higher enantioselectivity in related systems.^{7b-e} Using a more electron-rich ligand, (*S*)-*t*-BuPHOX, also sharply decreased the ee of the product (entry 11).

We then applied our optimal reaction conditions to a variety of diazepanone substrates (Scheme 3). First, the effect of the electronics of the lactam-protecting group on the reaction outcome was investigated. Switching from a benzoyl group (4b) to a more electron-poor *p*-CF₃-benzoyl group (4c) resulted in a slight increase in enantioselectivity. Interestingly, the use of an electron-rich *p*-anisoyl group delivered product 4d in an excellent 94% ee. It is worth noting that use of the *p*-anisoyl-protecting group was not beneficial to enantioselectivity in all cases (4a/4e, 4g/4h) and was often on par with the unsubstituted benzoyl group. A variety of functional groups at the quaternary carbon were tolerated, including groups bearing an alkenyl chloride (4f) and a *tert*-butyl carbamate (4i). This method also proved reliable for the formation of tertiary alkyl fluorides (4g, 4h). The low yield of propargyl lactam 4i and the necessity for elevated reaction temperatures are also noteworthy—allylic alkylation of other α -propargyl lactams studied by our group has proceeded smoothly.^{7e} It is possible that the geometry of the diazepanone substrate promotes coordination of the alkyne to palladium, hindering the desired reactivity. Additionally, this method allowed for the preparation of benzoyl lactam 4e on a 1 mmol scale, albeit in somewhat diminished yield and ee.

Having demonstrated the functional group tolerance of our methodology, we performed a short synthesis of an enantioenriched quaternary stereocenter-containing analogue of suvorexant, an FDA-approved sedative used to treat insomnia (Scheme 4). Diazepanone 4a was subjected to selective debenzoylation under basic conditions, followed by reduction with LiAlH₄ to yield diazepane 5 bearing a free secondary amine. Then, nucleophilic aromatic substitution of aryl bromide 6 with 5,¹¹ followed by Boc deprotection, with in situ generated HCl, furnished secondary amine 7. A final coupling with the benzoyl chloride derived from carboxylic acid 8¹¹ in the same pot provided target compound 9, an analogue of the drug suvorexant bearing an all-carbon quaternary stereocenter. The rapid synthesis of this drug analogue illustrates the ease with which *gem*-substituted diazepane units can be incorporated into pharmaceutically relevant molecules to produce new agents with potentially new biological properties.

We have demonstrated the use of palladium-catalyzed decarboxylative asymmetric allylic alkylation for the synthesis of enantioenriched *gem*-disubstituted diazepanones in up to >99% yield and up to 95% ee. Key to the high enantiomeric excess of this transformation is the use of the ligand (*S*)(CF₃)₃-*t*-BuPHOX and a nonpolar solvent, methylcyclohexane. This reaction tolerates a wide variety of functional groups (Scheme 3). In some cases, use of an electron-rich *p*-anisoyl lactam protecting group improves the enantioselectivity of this reaction.

As illustrated by our synthesis of suvorexant analogue 9, the chemistry reported herein can be easily adapted for the production of pharmaceutically relevant molecules bearing all-carbon quaternary stereocenters in a diazepane ring system. Future work will be dedicated to the generalization of the reported method to a wider array of complex heterocycles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Representative pharmaceuticals containing a diazepanederived ring system.

a) Synthesis of enantioenriched *N*-Boc diazaheterocycles

b) Synthesis of a chiral diazepanone in modest ee

c) This research: chiral *N*-Boc diazepanones in high enantioselectivity **Scheme 1.**

Enantioselective Decarboxylative Allylic Alkylation to Access α -Quaternary Diazaheterocycles

Scheme 2.
Methodology for the Synthesis of Substrates 3a-l

Scheme 3. Substrate Scope^a

^aReactions were performed on a 0.1 mmol scale at a 0.014 M concentration. An = *p*-anisoyl. ^bPd₂(pmdba)₃ was used instead of Pd₂(dba)₃. ^c1 mmol scale: 82% yield, 83% ee. ^dConducted at 50 °C for 17 h. ^ePerformed in 9:1 MeCy/toluene to improve substrate solubility.

Scheme 4.
Synthesis of a Suvorexant Analogue

Table 1.

Reaction Optimization^a

entry	solvent	ligand	ee ^b (%)
1	THF	(S)-(CF ₃) ₃ - <i>t</i> -BuPHOX	20
2	1,4-dioxane	(S)-(CF ₃) ₃ - <i>t</i> -BuPHOX	38
3	MTBE	(S)-(CF ₃) ₃ - <i>t</i> -BuPHOX	70
4	toluene	(S)-(CF ₃) ₃ - <i>t</i> -BuPHOX	66
5	2:1 hexanes/benzene	(S)-(CF ₃) ₃ - <i>t</i> -BuPHOX	84
6	2:1 hexanes/toluene	(S)-(CF ₃) ₃ - <i>t</i> -BuPHOX	87 ^c
7	cyclohexane	(S)-(CF ₃) ₃ - <i>t</i> -BuPHOX	88
8	cyclohexane	(S)-Ty-PHOX	80
9	MeCy	(S)-(CF ₃) ₃ - <i>t</i> -BuPHOX	89 ^c
10	2:1 MeCy/toluene	(S)-(CF ₃) ₃ - <i>t</i> -BuPHOX	86
11	MeCy	(S)- <i>t</i> -BuPHOX	50

^aScreening was performed on a 0.01–0.02 mmol scale. ^bValues determined by chiral SFC analysis. ^cAverage over 4 trials; values consistent within 1% ee.